Remarks

Claim listing

Claims 1-20 and 24-31 are pending in the application. No amendments are made at this time.

Declaration under 37 CFR §1.132 and Response to Final Office filed Feb. 11, 2009

With the filing of a Request for Continued Examination (RCE), Applicants request that the "Declaration of the Inventor Submitted with Response to a Final Office Action" under 37 CFR §1.132 by Dr. Frank Bergmann, filed on February 11, 2009, be entered. Applicants also note that the Response to Final Office Action filed on February 11, 2009 was entered according to the Advisory Action mailed February 27, 2009.

Claim rejections under 35 U.S.C. §103

Claims 1-20 and 24-31 stand rejected under 35 U.S.C. §103(a) as being unpatentable over previously cited Sheng-Hui et al., (WO 97/43451), in view of DeClercq et al. (U.S. 5,607,922) and Alexander et al. (U.S. 5,659,023), also previously cited. The rejections are respectfully traversed. MPEP 2142 states:

> The Examiner bears the initial burden of **factually supporting** any *prima facie* conclusion of obviousness. If the examiner does not produce a *prima facie* case, the applicant is under no obligation to submit evidence of nonobviousness. [emphasis added]

Applicants respectfully submit that the Office does not have the facts to support a *prima facie* case of obviousness as evidenced by several statements made in the Office Actions.

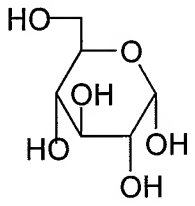
In both page 7 of the Office Action of 5/30/2008 and page 4 of the Office Action of 12/11/2008, the Office alleges:

> It would have been obvious to the ordinary skilled artisan to modify the reagents of Sheng-Hui et al. with the **substituted cyclohexene** (sp) **of DeClercq et al.** in the design of the instant invention. The ordinary skilled artisan would have been motivated to make this modification since Sheng-Hui et al. expressly teach that X^1 in the formula of their disclosed reagents preferably are substituted cyclohexane compounds [emphasis added].

This statement misstates a key fact known in the chemical arts which is that the 1,5 anhydrohexitol reagents disclosed both in DeClercq et al. and in the instant invention **are not substituted cyclohexanes.** It is well known to a skilled artisan in the field of organic chemistry that a "substituent" is an atom or group of atoms that are substituted in place of a **hydrogen atom** on the parent chain of a hydrocarbon (see e.g. Wikipedia in http://en.wikipedia.org/wiki/**Substituent**). Further factual evidence can be found in patent publications that clearly define "substituted cycloalkyls" as the replacement of one or more hydrogen atom in the hydrocarbon ring (see e.g. US 5,7356,549; US 7,482,301). Neither

Sheng-hui et al. nor DeClercq et al. nor any publication known to Applicants teaches or suggests that the family of substituted cyclohexanes may include molecules in which a carbon moiety in cyclic ring can be replaced by another atom such as oxygen to form 1,5 anhydroglucitol or 1,5 anhydromannitol (or any form of hexitol). Therefore, the Office's statement is not supported by facts.

Furthermore, on the chemical equivalence between cyclohexane and anhydrohexitol, the Declaration by Dr. Bergmann has clearly stated that they are not homologous. (See Decl., par. 8.) Again, it is well established in the chemical arts that cyclohexane and glucose (which has almost an identical structure to 1,5 anhydroglucitol as shown in the figure below) are not homologs and have vastly different chemical properties despite both being six-atom cyclical moieties. The inventor pointed out an additional critical difference: in Sheng-Hui et al.'s cyclohexane-based compounds, the functional groups necessary for chain elongation and oligonucleotide synthesis are connected to the same ring carbon, while in hexitol derivatives (such as De Clercq et al.'s or applicants' compounds) they are connected to different ring carbons. (See id.) Sheng-Hui et al. does not state or suggest to link the two functional moieties to two different ring carbon atoms. The inventor concluded that "a skilled chemist would not substitute one for another." (See id.)



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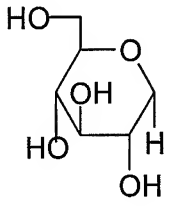

1,5 ANHYDROGLUCITOL

In page 3 of the Office Action of 12/11/2008, the Office states: "In the instant case, there is both structural similarity, and **a prior art recognized use for the disclosed compounds in the same methods set forth in the instant claims,** namely for the synthesis of oligonucleotides, and furthermore labeled nucleotide acids or oligonucleotides" [emphasis added]. Applicants respectfully note that in making this statement, the Office did not provide evidence as to which prior art reference actually teaches or suggests that the disclosed compounds are used "in the same methods as set forth in the instant claims". Both the Office and Applicants agree that De Clercq et al. does not teach or suggest the use of 1,5 anhydrohexitol compounds for the synthesis of oligonucleotides (or oligomeric

compounds) or for labeling oligomeric compounds used in hybridization of nucleic acids.[1] Therefore, the Office relies solely on the disclosure of Alexander et al. to support the argument that the prior art teaches the use of 1,5 anhydrohexitol for oligonucleotide synthesis or labeling. In page 3 of the Office Action of 09/07/2006, the Office states:

> Alexander et al. discloses nucleotide analogues, wherein said nucleotide analogues may comprise a 1,5-anhydrohexitol sugar base, and a modified pyrimidine or purine nucleobase (**see col. 1, lines 45-59**). According to Alexander et al. these nucleotide analogs are useful for the labeling of oligonucleotide probes (see col. 1, lines 65-66) [emphasis added].

Also, in page 7 of the Office Action of 05/30/2008, the Office alleges:

> As previously stated in a prior art rejection, Alexander et al. clearly contemplate the modification of of oligomeric structures with 1,5 anhydrohexitol sugars, **particularly as labeling reagents** [emphasis added]

Applicants respectfully submit that the facts in the disclosure of Alexander et al. do not support the Office's statements.

First, the nucleotide analogues disclosed in Column 1 of Alexander et al., including the 1,5 anhydrohexitol analogue on lines 45-59 [Formula (d)], are **not** claimed as the invention compounds of this patent but are rather cited as prior art compounds from Verheggen et al. J. Med. Chem. 36:2033-2040 (1993) which are clearly described as "**antiviral pyrans**" (col. 1, lines 25-26). There is no teaching or suggestion whatsoever in Alexander et al. that the antiviral pyrans disclosed in Verheggen et al. are useful for the labeling of oligonucleotide probes.

Second, although Alexander et al. discloses and claims a myriad of nucleotide analogues that have pyran (6-membered) or furan (5-membered) rings, and teaches that some these analogues possess antiviral activities (col. 72, EXAMPLE 21), it is completely silent with regards to analogues that may possess the other disclosed utilities such as preparation of fire retardant resins (col. 2, lines 1-2), anti-infective activity (col. 2, lines 3-4) and **the labeling of oligonucleotide probes** and polypeptides (col. 1, lines 65-66). It is unclear to Applicants what facts were used by the Office to support the asssertion that Alexander et al. contemplates the use of analogues that contain 1,5 anhydrohexitol sugars particularly as labeling reagents.

Applicants also respectfully note that in disclosing the use of their invention compounds for preparing labeled oligonucleotides, Alexander et al. teaches that if the

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[1] Office Action of 09/07/2006, page 3: "Additionally, DeClerq et al. do not teach wherein the disclosed 1,5-anhydrohexitol nucleoside analogues can be used as a monomeric componenet (sp) of an oligomeric compound." Applicants' Response of 02/11/2009, page 11-12: "The purpose of De Clercq is to administer a single nucleoside to a virus in order to block replication of the virus. Neither reference mentions or suggests that antiviral nucleosides are suitable for incorporation into nucleic acids in general or labeled oligonucleotides in particular."

compounds "contain a free hydroxyl group (ordinarily one or both of the R1 groups or Z) linked to the pyran or **(preferably) the furan ring,** they optionally are incorporated internally into the sequence of the oligonucleotide" (col. 36, lines 63-67) [emphasis added]. In other words, there is a suggestion in Alexander et al. that for use in labeling oligonucleotides, compounds that have five-membered sugar rings are preferred over compounds that have six-membered sugar rings, such as the 1,5 anhydrohexitol compounds of the present invention. When combined with the arguments set forth above regarding 1,5 anhydrohexitol compounds being described only as antiviral pyrans, Applicants respectfully submit that Alexander et al. actually teaches away from the claims of the instant invention.

In summary, Applicants have provided factual evidence that: a) 1,5 anhydrohexol is not a substituted cyclohexane and b) Alexander et al. either is silent or teaches away from the instant claims. Because the Office relied on arguments that are not factually supported, Applicants respectfully submit that a *prima facie* case of obviousness has not been established. Applicants respectfully request that the rejections of Claims 1-20 and 24-31 under 35 U.S.C. §103(a) be withdrawn.

Conclusion

It is believed that all claims are now in condition for allowance. The Commissioner is authorized to charge the RCE fee under 37 CFR 1.17(e) required for this submission to Deposit Account No. 50-0812. No other fee is believed to be due at this time, however, the Commissioner is authorized to charge any fee deficiency, or credit any overpayment, to the deposit account indicated above.

If the Examiner believes that a telephone conference would expedite prosecution of this application, please call the undersigned directly at the number below.

Respectfully submitted,

Date: March 10, 2009

David J. Chang (Reg. No. 50,374)

Roche Molecular Systems, Inc.
4300 Hacienda Drive
Pleasanton, CA 94588
Tel: (650) 855-5316
Fax: (650) 855-5322